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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,997	09/18/2003	Carol Carter	70017.0017USC1	6642

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,997	CARTER ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-91 and 93-131* is/are pending in the application.

4a) Of the above claim(s) *59-91 and 95-131* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93 and 94* is/are rejected.

7)☒ Claim(s) *93 and 94* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office acknowledges the receipt of Applicant's election and Amendment, filed on 30 November 2006. Claims 1-58 and 92 have been cancelled.

Election/Restriction

Applicant elects Group VI, claims 93 and 94, with traverse. The traversal is on the grounds that there is no search burden in examining the different inventions together. Applicant's traversal is not persuasive for the following reasons:

There are different limitations in each Group that require a separate search. The search for more than one group presents a serious burden on the office as art relating to the products in Group I and IV will not necessarily provide any information regarding the methods in Group II, III, V and VI, while such methods will not necessarily provide any structural information pertaining to the all of the products encompassed by the claims in Group I and IV. While a search of the prior art for one Group may overlap with that of another group, the searches are not co-extensive and thus would be an undue burden on Office resources.

Furthermore, Applicant is no longer entitled to the rejoinder of the process claims with the product claims because Applicant has elected the process claim. See *In re Ochiai, In re Brouwer.*

The restriction among the different products that may be used in the claimed methods is maintained. The requirement is still deemed proper and is therefore made FINAL.

Claims 59-91 and 93-131 are pending. Claims 59-91 and 95-131 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction

(election) requirement in the reply filed on 30 November 2006. Claims 93 and 94 are under examination. No claim is allowable.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, filed on 07 March 2005, is attached to the instant Office action.

Claim Objections

Claims 93 and 94 are objected to because of the following informalities: each of these claims refers to the proteins TSG101 by its acronym without first identifying it by the full names, tumor susceptibility gene 101. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st ¶, written description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 93 and 94 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention*. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M.P.E.P. §2163.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 199 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly & Co.,* the court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus.

Although the M.P.E.P. does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method of inhibiting HIV budding, treating HIV infection or preventing AIDS comprising administering a compound that binds TSG101 protein. The claims read on a genus of compounds that bind Tsg101 proteins, which encompass siRNA, aptamers, ribozymes, antibodies, small molecule inhibitors, and Gag homologs. The claims encompass an inordinate number of species that are neither described nor contemplated by Applicants.

The only factor present is the Pr55 Gag p6 L domain with a PTAPP motif (Example 1). The specification neither describes any key molecular determinants in TSG101 for targets, nor describes any TSG101-binding motif on each species of the claimed genus. For example, the specification nowhere discloses a critical epitope on the antibody for TSG101, a binding region on the trans-dominant mutants, or a TSG101-binding conformational region on the peptide or peptidomimetic inhibitor.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states: "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* on page 1116).

The instant application is highly analogous to the *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). Patent is directed to a method for inhibiting prostaglandin synthesis in human host using unspecified compound. Action by University of Rochester against G.D. Searle & Co. Inc., Monsanto Co., Pharmacia Corp., and Pfizer Inc. for patent infringement. District court granted defendants' motion for summary judgment of patent invalidity based on failure to satisfy written description and enablement requirements, and plaintiff appealed. Affirmed.

While the specification adequately describes a method of inhibiting HIV budding in cell culture by administering Gag p6 late domain containing the PTAPP motif, this does not constitute a representative number of species to adequately describe the broad genus of unspecified Tsg101 binding compounds. As a result, one of skill in the art could not conclude that Applicant was in possession of the claimed method at the time of the invention. Therefore, claims 93 and 94 do not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (page 1115).

Claim Rejections - 35 USC § 112, 1st ¶, enablement

Claims 93, 94 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for inhibiting HIV budding in cell culture by administering Gag p6 L domain comprising the PTAPP motif, does not reasonably provide enablement for other unspecified TSG-101 binding compounds as HIV inhibitors or treatment of HIV infection or prevention of AIDS in patients. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention

commensurate in scope with these claims. Enablement is considered in view of the *Wands* factors (MPEP §2164.01(a)).

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Nature of the invention. The claims are drawn to a method of inhibiting HIV budding, treating HIV infection or preventing AIDS comprising administering a compound that binds TSG101 protein.

Breadth of the claims. The claims read on a genus of unspecified compounds that bind Tsg101 proteins, which encompass siRNA, aptamers, ribozymes, antibodies, small molecule inhibitors, and Gag homologs. The claims are of excessive breath and encompass any give putative antiviral compound without providing any meaningful structural limitations concerning that compound. The disclosure simply fails to support such breadth in the claim language.

Working examples. The disclosure fails to provide any working embodiments that meet the claimed limitations. While there is one cell culture example is disclosed for the species of Gag p6 late domain, this compound does not represent all other TSG101-inhibitors that fall

within the scope of the invention. There are no other examples of TSG101-binding compounds. No *in vivo* working example of any TSG101-binding compound is disclosed in the specification.

Guidance in the specification. The specification provides no guidance regarding practice of the claimed method. The amount of direction is limited to a cell culture assay to determine the binding between HIV Gag p6 late domain and Tsg101 (Example 1) and the amount of mature HIV particles (Example 2). There is no evidence that shows any correlation with *in vivo* efficacy. First of all, there is no structural guidance to the broad genus of unspecified TSG101-binding inhibitors. In other words, the specification fails to disclose which chemical structures are critical for binding to TSG101 and which structures are required for anti-HIV budding. Thus, the specification is no more than an undue invitation by the applicant to further experimentation to identify putative HIV budding inhibitors and determine their structures. Second, there is no teaching about the therapeutic properties such as the binding specificity, selectivity and affinity, oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects. Lastly, there is not even a test to determine the efficacy and resistance of the claimed genus of Tsg101 inhibitors to confirm the cell culture inhibitory results. *In vitro* testing is, at most, a useful tool for screening potential anti-viral agents but is not predictive of *in vivo* effectiveness. *Ex parte Balzarini* (BdPat App&Int) 21 USPQ2d 1892. One skilled in the art would not associate successful *in vitro* testing results with successful *in vivo* AIDS treatment without any knowledge of the pharmacokinetic profile, therapeutic and/or prophylactic effect in a patient. Therefore, the disclosure does not correlate with treating HIV infection or preventing AIDS, especially when the subject may be a person.

State of the prior art. At the time the invention was made, a TSG101 binding compound for the treatment of HIV is not considered routine in the art. It has been well known

in the prior art (Hendrix, 2000, 1st and last ¶; Gait, 1995) that the development of suitable HIV-1 therapeutics has been an arduous and empirical process, often ending in failure. This is due to a number of factors: (1) failure to understand the molecular determinants modulating many viral protein and host cell factor interactions; (2) failure of in vitro tissue culture studies and in vivo animal models to adequately predict clinical efficacy; (3) failure of many compounds to have acceptable pharmacological profiles despite initial favorable in vitro and in vivo activities; and (4) failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The challenges of developing efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state in the Conclusions (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

Predictability of the art. The art of HIV treatment is highly unpredictable because the effect of antiretroviral treatment appears to change due to pharmacokinetic variation, fluctuating adherence, the emergence of drug resistant mutations and/or other factors. Inadequate drug concentrations can result from a number of factors including non-adherence,

pharmacokinetics, and lack of drug potency. In addition, anatomical sanctuary sites may exist where drug concentrations do not achieve adequate levels despite apparent therapeutic serum drug concentrations. HIV replication can occur in such settings, and the selective pressure of antiretroviral therapy leads to the emergence of HIV harboring drug-resistant mutations. Thus, a key element in future drug design strategies is to understand how drug resistance mutations affect the interaction of the drug with its target, and to then develop compounds with the adaptability to inhibit these variants along with wild-type HIV (Yin, 2006). Therefore, efforts to develop effective treatments must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

Amount of experimentation necessary. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case, a Tsg101 inhibitor as a HIV drug is not considered routine in the art. The disclosure fails to address any of the aforementioned caveats in the development of an antiviral agent. Without sufficient guidance to the safety, tolerability, and antiviral effect, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances.

For the reasons discussed above, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for

> patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 93 and 94 are rejected under 35 U.S.C. §102(e) as being anticipated by Zavitz *et al.* (US 2004/0109861, effectively filed 14 March 2001).

The instant claims are directed to a method of inhibiting HIV budding or treating HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound which binds TSG101 protein.

Zavitz *et al.* teach methods for inhibiting HIV viral budding and treating HIV infection by binding Tsg101 with a retroviral HIV GAG containing a P(T/S)AP late domain motif. See page 5, ¶72. For example, it has been discovered that a contiguous span of 8 amino acids in the late domain region of HIV GAGp6 (PEPTAPPEE, SEQ ID NO:22) is effective in inhibiting HIV viral budding. See page 33, ¶294. Thus, Zavitz *et al.* clearly anticipates the invention.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
06 February 2007

Louise Humphrey, Ph.D.
Assistant Examiner